Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: C: Detailed analysis of trial of lapatinib in combination with capecitabine in advanced, HER2+ breast cancer leads to marketing authorisation worldwide

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare; additional effective therapy for women with advanced, HER2+ breast cancer.

Significance: Allows approximately 10,000 patients a year, whose disease is no longer being controlled by trastuzumab, to receive a more effective therapy than chemotherapy with capecitabine alone.

Beneficiaries: Patients with incurable metastatic HER2+ subtype breast cancer; policy-makers; commerce.

Attribution: Cameron (UoE) was joint chief-investigator on the global pivotal registration trial that led to the marketing authorisation of the drug lapatinib in combination with capecitabine.

Reach: World-wide: the drug is approved in >100 countries and generated >£650M in sales for manufacturer GlaxoSmithKline.

2. Underpinning research (indicative maximum 500 words)

Professor David Cameron (part-time Honorary Senior Lecturer in Oncology, UoE, since 2003; appointed to Professor of Oncology, 2009), as joint global Chief Investigator, undertook the detailed analysis of sub-group outcomes that identified cohort benefit in advanced metastatic breast cancer in the capecitabine and lapatinib HER2+ metastatic breast cancer trial [3.1]. Crucially, further analyses of the trial data by Cameron and colleagues identified evidence that there might be a subgroup of patients who particularly benefited from the addition of lapatinib. Circulating serum markers and tumour characteristics failed to identify patients who did not benefit from the use of lapatinib [3.2–3.4], other than those whose tumours were not centrally confirmed to be HER2-over-expressing.

The chance of a woman having invasive breast cancer some time during her life is about one in eight. Around 12–15% of all breast cancers over-express the cell surface tyrosine kinase receptor human epidermal growth factor receptor 2 (HER2+). These patients have more aggressive disease than those who are HER2-negative, and a higher chance of developing incurable, life-threatening metastatic disease. The drug trastuzumab (Herceptin) is used to treat such cases, but in most patients, resistance develops and alternative therapies are needed. No such therapies were available before the development of lapatinib.

After preliminary pre-clinical, phase I and phase II studies that confirmed the efficacy of lapatinib in previously treated HER2+ metastatic breast cancer, and demonstration of an acceptable tolerability profile when combined with the chemotherapy agent capecitabine, it was clear that there was real potential for this combination to be effective in treating metastatic breast cancer that overexpressed HER2 and was no longer responding to trastuzumab (Herceptin). In liaison with colleagues at GlaxoSmithKline (GSK), Cameron (who assumed the role of joint global chief investigator for the work while Honorary Senior Lecturer at UoE) led a multinational, multicentre randomised phase III trial to test the hypothesis that the combination of lapatinib and the cytotoxic drug capecitabine would be superior to capecitabine alone in patients with HER2+ metastatic breast cancer that had progressed despite trastuzumab treatment. Trial design and execution was closely aligned to FDA requirements to maximise the opportunity to bring a new treatment to the clinic rapidly. Patients were recruited in 2004–2006 and the Independent Data Monitoring

Committee (IDMC) reviewed an interim analysis of the study in March 2006, and recommended that the trial be stopped and patients allowed to cross over to the research arm. The interim analysis data were published in late 2006 [3.1]. The data-set that was used for the European (and many other countries') application for marketing authorisation was the analysis of all enrolled patients that was published in 2008 [3.2].

The trial showed that the time to disease progression (worsening of the cancer) almost doubled in patients with HER2+ advanced breast cancer treated with lapatinib in combination with capecitabine compared with the use of capecitabine alone, with median times to progression significantly better in the combination arm (8.4 months) compared with the single arm (4.4 months) ($p < 0.001$, hazard ratio = 0.47). In addition there was evidence of a higher rate of tumour shrinkage (objective response rate) on the combination therapy with a 22% response rate, while the response to capecitabine alone was 14% ($p = 0.09$).

Data on quality of life for patients on this therapy [3.5], and a final survival analysis [3.6] have also been published. These report that there are quality of life benefits, despite the modest toxicity, as well as some evidence of a survival benefit for those patients being offered this combination after only one trastuzumab-containing regimen for metastatic breast cancer.

3. References to the research (indicative maximum of six references)

3.1 Geyer C, Forster J, Lindquist D,…Cameron D. Lapatinib plus capecitabine compared with capecitabine alone for HER2-positive advanced breast cancer. New Eng J Med. 2006;355:2733–43. DOI: 10.1056/NEJMoa064320.

3.2 Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112:533–43. DOI: 10.1007/s10549-007-9885-0.

3.3 Press M, Finn R, Cameron D, et al. HER-2 gene amplification, HER-2 and epidermal growth factor receptor mRNA and protein expression, and lapatinib efficacy in women with metastatic breast cancer. Clin Cancer Res. 2008;14:7861–70. DOI: 10.1158/1078-0432.CCR-08-1056.

3.4 Scaltriti M, Chandarlapaty S, Prudkin L,…Cameron D, et al. Clinical benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor 2-positive breast tumors coexpressing the truncated p95HER2 receptor. Clin Cancer Res. 2010;16:2688–95. DOI: 10.1158/1078-0432.CCR-09-3407.

3.5 Zhou X, Cella D, Cameron D, et al. Lapatinib plus capecitabine versus capecitabine alone for HER2+ (ErbB2+) metastatic breast cancer: quality-of-life assessment. Breast Cancer Res Treat. 2009;117:577–89. DOI: 10.1007/s10549-009-0310-8.

3.6 Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15:924–34. DOI: 10.1634/theoncologist.2009-0181.

4. Details of the impact (indicative maximum 750 words)

The widespread adoption of lapatinib as a combination agent for advanced breast cancer hinged on the detailed analysis of sub-groups led by Cameron (3.2–3.4). The results of the phase III trial with lapatinib confirmed the clinical efficacy of a small molecular tyrosine kinase inhibitor in patients with HER2+ breast cancer for which trastuzumab was no longer effective. Lapatinib was the first agent to be approved for use in HER2+ breast cancer after trastuzumab.

Impact on health and welfare

There are no robust data available on the number of patients treated with lapatinib, but it is likely to be around 10 000 or more each year, based on the drug costs and average duration of therapy. For women with advanced HER2+ breast cancer, who without effective therapy have a poor

prognosis, the use of lapatinib plus capecitabine offers an entirely oral, effective therapy once the disease has become resistant to trastuzumab, which is the first-line therapy. The treatment is not curative — cures are rare in metastatic breast cancer — but it delivers clear clinical benefits for patients. Also, because of the availability of lapatinib, a phase II study compared radiotherapy with capecitabine plus lapatinib, and confirmed that this combination was an equally effective alternative to conventional radiotherapy for treating patients with HER2+ breast cancer metastatic to the brain [5.1].

Impact on commerce and the economy

Lapatinib generated sales for the UK-based company (GSK) of £227M in 2010, £231M in 2011 and £239M in 2012 [5.2]. In addition, but hard to quantify, there are economic benefits of an effective therapy for patients with advanced breast cancer – some are able to continue working because their disease is being better controlled.

Impact on public policy

The positive results of this pivotal, registration phase III trial led to marketing authorisations in 107 countries including the USA, Europe, Australia, India, Brazil, Russia, Turkey, South Korea and other countries around the world [5.3]. The majority of these authorisations have occurred after 1st Jan 2008; for example, the European Commission granted a conditional marketing authorisation for lapatinib in all 27 European Union (EU) member states on June 10, 2008 [5.4]. The option of using lapatinib in combination with capecitabine is recommended within a number of guidelines (e.g., European School of Oncology, German Gynecological Oncology Group (Arbeitsgemeinschaft Gynaekologische Oncologie, AGO), National Comprehensive Cancer Network (NCCN) guidelines in the USA and European Society for Medical Oncology (ESMO) guidelines [5.5, 5.6, 5.7]). Although it is licensed in the UK, the regimen was not approved by either the National Institute for Health and Care Excellence (NICE) or the Scottish Medicines Consortium (SMC), as it was felt to be insufficiently cost-effective. Denial to fund this treatment led to intensive patient-led campaigning, and the lapatinib-treatment-seeking patient Nikki Blunden, whose case was highlighted in the House of Commons (June 16, 2010), became “the face” of the Government’s £50M emergency fund to pay for new cancer drugs for those with life-shortening cancer [5.8]. From October 2010 until February 2011, 195 patients obtained lapatinib treatment due to the interim cancer drugs funding, and from April until September 2011 more than 350 patients received the drug with support from the Cancer Drugs Fund [5.9]. Lapatinib used in this indication is one of the top ten drugs within the English Cancer Drugs’ fund with an approval rate of 94% (June 2011) [5.10], reflecting strong UK clinician support for the treatment whose efficacy was confirmed by the phase III trial.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER-2 positive metastatic breast cancer (LANDSCAPE): a single group phase 2 study. Lancet Oncol. 2013;14:64–71. DOI: 10.1016/S1470-2045(12)70432-1.

5.2 GSK Annual Report 2012. http://www.gsk.com/investors/annual-reports/annual-report.html.

5.3 Lapatinib clinical trial update, GSK press release issued on 9 Sep 2011. http://us.gsk.com/html/media-news/pressreleases/2011/2011-pressrelease-614856.htm.

5.4 European Medicines Agency (EMA) marketing authorisation for European Union. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000795/human_med_001120.jsp&mid=WC0b01ac058001d124.

5.5 Cardoso F, Costa A, Norton L, et al. 1st international consensus guidelines for advanced breast cancer (ABC1). Breast. 2012;21:245–52. DOI: 10.1016/j.breast.2012.03.003.

5.6 USA NCCN guidelines. http://www.nccn.org/patients/guidelines/breast/index.html#/93/zoomed.

5.7 ESMO guidelines. http://www.esmo.org/Oncology-News/The-European-Medicines-Agency-Extends-Indications-for-Lapatinib.

5.8 Daily Mail, April 12, 2011. “Cancer mother who fulfilled wish to see her son start school loses fight for life”. http://www.dailymail.co.uk/health/article-1376007/Lapatinib-drug-campaigner-Cancer-mother-campaigned-fund-donor-paid-drug-help-son-school-loses-fight-life.html.

5.9 Breast Cancer Campaign report (November 2011). “The cancer drugs fund: a breast cancer perspective”. http://www.breastcancercampaign.org/documents/policy/cancer-drugs-fund-a-breast-cancer-perspective.pdf.

5.10 Macmillan Cancer Support report (December 2011). “Improving Access? Report on the implementation of the Cancer Drugs Fund and the development of a value-based pricing system”. http://www.macmillan.org.uk/Documents/GetInvolved/Campaigns/Campaigns/CancerDrugFund/ImprovingAccess.pdf.